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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE BOARD OF PATENT APPEALS
AND INTERFERENCES

Ex parte ZSUZSANNA NAGY

Appeal 2009-012158
Application 10/659,578
Technology Center 1600

Decided: July 1, 2010

Before DONALD E. ADAMS, LORA M. GREEN, and
JEFFREY N. FREDMAN, *Administrative Patent Judges*.

FREDMAN, *Administrative Patent Judge*.

DECISION ON APPEAL

This is an appeal under 35 U.S.C. § 134 involving claims to a method for diagnosing Alzheimer's Disease. We have jurisdiction under 35 U.S.C. § 6(b). We affirm.

Statement of the Case

The Claims

Claims 1-3, 5, 6, 8, 17, 30-32, and 34 are on appeal. Claim 1 is representative and reads as follows:

> 1. A method for the diagnosis of a neurological condition in a human subject, wherein said neurological condition is selected from the group consisting of: Alzheimer's Disease; incipient Alzheimer's Disease; possible Alzheimer's Disease; and Alzheimer's Disease associated with evidence of other type of dementia; wherein said method comprises the steps of:
>
> (A) determining the effectiveness of the G1/S cell cycle checkpoint exhibited by a non-neuronal cell of said subject; and
>
> (B) comparing said determined G1/S cell cycle checkpoint effectiveness with the G1/S cell cycle checkpoint effectiveness exhibited by a non-neuronal reference cell of a healthy individual or of an individual having said neurological condition, to thereby diagnose whether said subject has said neurological condition.

The prior art

The listing of the prior art relied upon by the Examiner is found in the Examiner's Answer (*see* Ans. 2-3).

The issues

A. The Examiner rejected claims 1-3, 5, 6, 8, 17, 30-32, and 34 under 35 U.S.C. § 112, first paragraph, enablement (Ans. 4-9).

B. The Examiner rejected claims 1-3, 5, 6, 8, 17, 30-32, and 34 under 35 U.S.C. § 112, first paragraph, new matter (Ans. 9-10).

A. 35 U.S.C. § 112, first paragraph, Enablement

The Examiner finds that "merely assaying for a defect in the G1/S checkpoint, or relative resistance to the effects of a G1 inhibitor such as rapamycin, then diagnosing patients with such a G1/S defect as having AD would misdiagnose many cancer patients as having AD" (Ans. 7). The Examiner finds that:

> Applicants provide no direction or guidance for diagnosing AD, or any other neurological condition, by performing only the method steps as instantly claimed (e.g. see claim 1). The specification requires the skilled artisan to practice trial and error experimentation to develop a reliable and effective assay that differentiates AD from other dementias and cancer by merely assaying for a G1/S checkpoint defect.

(*Id.* at 8.)

Appellant argues that, based on the Nagy Declaration, the diagnostic method of the Specification "is as reliable as other diagnostic methods in the art, there is no contradictory data, and there is sufficient guidance both in the Application and in the general knowledge of those skilled in the art to enable the diagnosis of the recited neurological diseases using the claimed methods" (App. Br. 5). Appellant argues that the Specification teaches "working examples describing the use of the claimed methods to diagnose Alzheimer's Disease and the other recited neurological diseases, which diagnosis *was confirmed by* the independent diagnosis of the patients using the NINCDS-ARDRA criteria" (*id.* at 6).

Appellant also argues, based on the Nagy Declaration, that "use of the claimed methods would not lead to misdiagnoses" (*id.* at 7). Appellant argues that "Dr. Nagy stated that those skilled in the art would recognize the

ability of the claimed methods to predictably diagnose Alzheimer's Disease prior to death, at a reliability comparable to currently used diagnostic methods" (App. Br. 9).

In view of these conflicting positions, we frame the enablement issue before us as follows:

Does the evidence of record support the Examiner's conclusion that undue experimentation would have been required to perform the claimed diagnostic test for Alzheimer's Disease?

Findings of Fact (FF)

Breadth of Claims

1. Claim 1 is drawn to diagnosis in *any* human subject of Alzheimer's Disease, incipient Alzheimer's Disease, possible Alzheimer's Disease and Alzheimer's Disease associated with evidence of other types of dementia (*see* Claim 1).

2. Claim 1 comprises a method of determining the effectiveness of the G1/S cell cycle checkpoint in *any* non-neuronal cell of a subject relative to healthy or diseased controls using *any* checkpoint inhibitor (*see* Claims 1 and 3).

Presence of Working Examples

3. The Specification teaches analyzing the lymphocytes of 104 subjects by treating the lymphocytes with or without rapamycin and measuring "relative lengthening of the G1 phase of the cell cycle in treated cultures relative to control cultures" (Spec. 24, ll. 24-26).

4. The Specification teaches that:

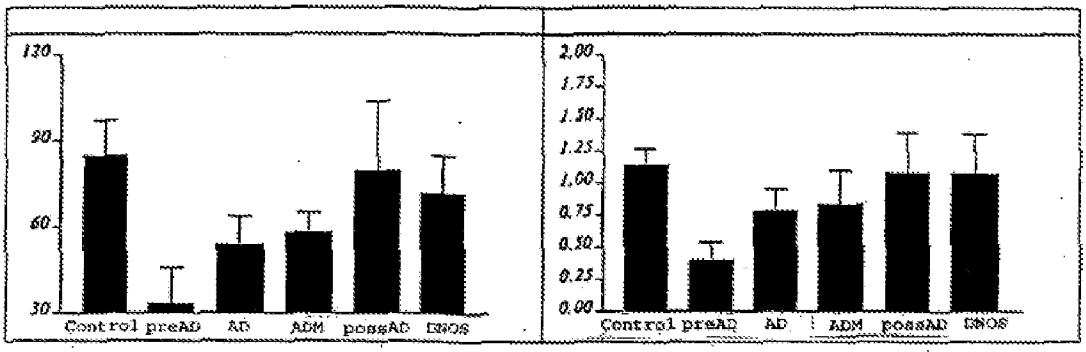
> The highest values, indicating more effective G1 inhibition by rapamycin, were found in subjects diagnosed as controls,

> dementia syndromes other than AD and possible Alzheimer's disease patients. Patients diagnosed as suffering from AD (probable AD by NINCDS) and those with AD and coexisting other pathology (ADM) were found to have a significantly less effective G1 block than control subjects and patients suffering from DNOS or possAD as diagnosed by the NINCDS criteria.

(Spec. 26, ll. 6-16.)

5. Figure 2 of the Specification is reproduced below:

Figure 2. Relative and age-corrected relative lengthening of the G1 phase under the influence of Rapamicin.



"Figure 2 illustrates relative (left panel) and age- corrected relative (right panel) lengthening of the G1 phase of the cell cycle under the influence of rapamycin in cultured lymphocytes from preAD, AD, ADM, possAD, DNOS and control subjects" (Spec. 21, ll. 21-25).

6. The Specification teaches that DNOS is defined as "patients with dementia who do not meet the requirements of the NINCDS criteria for probable Alzheimer's disease" (Spec. 27, ll. 31-32).

Amount of Direction or Guidance Presented

7. The Specification teaches that when "the method of the invention is used diagnostically, the presence of a defect in cell cycle

regulation at the G1/S phase transition in a non-neuronal cell type is taken as an indication that the subject has Alzheimer's disease" (Spec. 4, ll. 25-29).

8. The Specification teaches screening lymphocytes as the non-neuronal cell type (*see* Spec. 5, l. 9).

9. The Specification teaches methods of performing the proliferation assay as well as calculating the lengthening of the G1 phase of the cell cycle which results from exposure to a cell division inhibitor or stimulus that induces cell cycle arrest (*see* Spec. 8-10).

State of the Prior Art and Unpredictability of the Art

10. The Specification teaches that a "definite diagnosis of Alzheimer's disease can only be made after post mortem examination" (Spec. 5, ll. 4-6).

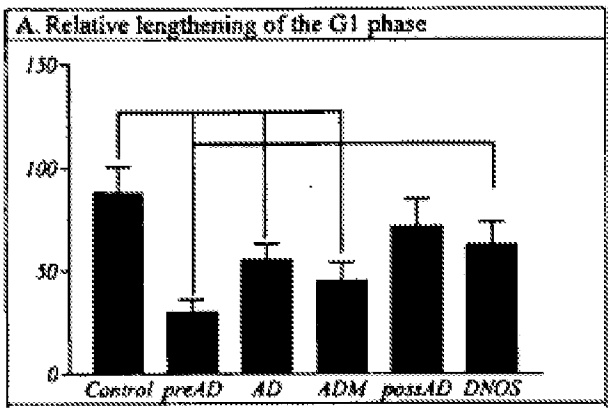
11. Wendel teaches that "rapamycin reverses the apoptotic defects and drug resistance occurring in Akt lymphomas . . . although each lymphoma studied contained an anti-apoptotic lesion, the chemosensitizing effects of rapamycin were specific for tumours with constitutive Akt signalling [sic]" (Wendel 334, col. 1).

12. Chan teaches that "mammalian cells display widely varying sensitivities to the growth-inhibition of rapamycin. A typical target cell for rapamycin is the activated T lymphocyte, which undergoes G1 to S phase progression in response to IL-2 or T-cell growth-promoting cytokines" (Chan 1421, col. 1).

13. Chan teaches that a "study of a panel of breast cancer cell lines showed differences in the sensitivity to the antiproliferative effects of CCI-779 [a rapamycin analogue]" (Chan 1421, col. 2).

14. The Examiner finds that "in Fig. 1A of Nagy et al (2002), the DNOS group is less responsive to rapamycin than the control. According to the instantly claimed methods, this would lead to a misdiagnosis of these patients as having AD, which is clearly not correct" (Ans. 6).

15. Figure 1, panel A of Nagy (2002) is reproduced below:



This figure shows the relative lengthening of the G1 phase in control patients and patients with various Alzheimer's disease diagnoses and DNOS patients, who have dementia but do not meet the requirements of the NINCDS criteria for probable Alzheimer's disease.

16. Nagy (2002) teaches that "while the rapamicin [sic] induced a significant lengthening of the G1 phase after 24 h, the effects on cell numbers are not robust enough to discriminate between AD patients and control subjects" (Nagy (2002) 83, col. 2).

17. Ichimura teaches that "[a]bnormalities of genes involved in G_1-S transition and the p53 pathway are frequently found in different human tumors" (Ichimura 422, col. 2).

Quantity of Experimentation

18. The Examiner finds that the "specification requires the skilled artisan to practice trial and error experimentation to develop a reliable and

effective assay that differentiates AD from other dementias and cancer by merely assaying for a G1/S checkpoint defect" (Ans. 8).

Skill in the art

19. The Examiner finds that "[w]hile the level of skill in the art of assaying for cell cycle defects is high, the level of skill in the art of diagnosing AD by assaying for such defects is low" (Ans. 9).

Principles of Law

> When rejecting a claim under the enablement requirement of section 112, the PTO bears an initial burden of setting forth a reasonable explanation as to why it believes that the scope of protection provided by that claim is not adequately enabled by the description of the invention provided in the specification of the application.

In re Wright, 999 F.2d 1557, 1561-62 (Fed. Cir. 1993). "[T]he question of undue experimentation is a matter of degree. The fact that some experimentation is necessary does not preclude enablement; what is required is that the amount of experimentation 'must not be unduly extensive.'" *PPG Indus., Inc. v. Guardian Indus. Corp.*, 75 F.3d 1558, 1564 (Fed. Cir. 1996).

> Factors to be considered in determining whether a disclosure would require undue experimentation … include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

In re Wands, 858 F.2d 731, 737 (Fed. Cir. 1988).

Analysis

Claim interpretation is at the heart of patent examination because before a claim is properly interpreted, its scope can not be compared to the prior art. In this case, a central aspect of the dispute centers on the claim requirement for "diagnosis."

During prosecution, claim terms are given their broadest reasonable interpretation as they would be understood by persons of ordinary skill in the art in the light of the Specification. Therefore, we first turn to the Specification to determine whether the scope of the term "diagnosis" can be discerned. The Specification teaches that the invention is "early diagnosis of Alzheimer's disease, especially detection of individuals who are in pre-clinical stages of the disease, and for identification of individuals who have not yet developed Alzheimer's disease as such but are 'at risk' of doing so because of the presence of the cell cycle regulatory defect" (Spec. 5, ll. 11-17).

Therefore, we interpret the "diagnosis" in the context of Claim 1 as identifying individuals with clinical, pre-clinical, or possible Alzheimer's Disease.

The Examiner's argument is that a method for "diagnosis of a neurological condition . . . selected from . . . Alzheimer's Disease; incipient Alzheimer's Disease; possible Alzheimer's Disease; and Alzheimer's Disease associated with evidence of other types of dementia" requires that the method function to reliably distinguish individuals with Alzheimer's based neurological conditions from individuals with cancer or dementia other than Alzheimer's Disease (*see* Ans. 5-6). The Examiner explains that

there is "no certain way to differentiate such a result between a diagnosis of cancer or one of the recited neurological conditions" (Ans. 5). The Examiner also finds that "the DNOS group is less responsive to rapamycin than the control. According to the instantly claimed methods, this would lead to a misdiagnosis of these patients as having AD, which is clearly not correct" (*id.* at 6).

Appellant argues, based on the Nagy Declaration, that the diagnostic method of the Specification "is as reliable as other diagnostic methods in the art, there is no contradictory data, and there is sufficient guidance both in the Application and in the general knowledge of those skilled in the art to enable the diagnosis of the recited neurological diseases using the claimed methods" (App. Br. 5).

We find that the Examiner has the better position. The evidence of record supports the Examiner's conclusion that the claimed method does not distinguish between the DNOS patient population and the various Alzheimer's patient populations (FF 4-16). Both Figure 2 of the Specification (FF 5) and Figure 1, Panel A of Nagy (2002) (FF 16) show that the DNOS patient population, a group defined by the Specification as having non-Alzheimer's disease dementia, would be diagnosed by the method of the instant claims as having Alzheimer's Disease (FF 5-6, 15-16).

The evidence of record also supports the Examiner's conclusion that the claimed method would not reliably distinguish between non-neuronal cells of certain cancers and Alzheimer's Disease, as shown by Wendel, Chan and Ichimura (FF 11-13, 17-18).

Thus the Examiner has reasonably concluded that undue experimentation would be required to use the instantly claimed method for "diagnosis of a neurological condition . . . selected from . . . Alzheimer's Disease; incipient Alzheimer's Disease; possible Alzheimer's Disease; and Alzheimer's Disease associated with evidence of other types of dementia" since the method will not reliably distinguish the spectrum of Alzheimer's Disease patients from DNOS patients or certain cancer patients.

Appellant argues that "because cancer does not produce the cell cycle effects used in the claim methods in *non-cancerous cells*, use of the claimed methods would not lead to misdiagnoses" (Ans. 7). Appellant cites the Nagy Declaration, which states that "like any other diagnostic method, the claimed method enables (but does not mandate) the diagnostic practitioner skilled in the art to make a diagnostic conclusion based on the results of the method" (Nagy Dec. B-7 ¶ 18).

We are not persuaded since the argument is inconsistent with the express scope of the claims as written. That is, Claim 1 does not state that the method is "indicative of a neurological condition . . ." or that the method shows "increased risk of a neurological condition . . .," but directly mandates (to use the Nagy Declaration's term) that if there is decreased effectiveness of a G1/S cell cycle checkpoint relative to a normal control, the patient is diagnosed with Alzheimer's Disease (*see* Claim 1). Claim 1 includes no language to suggest the use of other diagnostic information to determine the required "diagnosis." "[L]imitations are not to be read into the claims from the specification." *In re Van Geuns*, 988 F.2d 1181, 1184 (Fed. Cir. 1993) (citing *In re Zletz*, 893 F.2d 319, 321 (Fed. Cir. 1989)).

Thus Claim 1 encompasses the situation where a patient with DNOS or with cancer would submit a sample for analysis, which analysis would reasonably result in a misdiagnosis based upon the claimed method (FF 10-18).

Appellant argues regarding the issue of the Nagy (2002) data and the data in the Application that the "Examiner dismisses these arguments set forth in the Nagy Declaration with little explanation" (App. Br. 11).

We disagree. The Examiner directly addressed the Nagy Declaration's data analysis (*see* Final Rej. 5). More importantly, the data in the Nagy Declaration does not detract from the Examiner's fundamental point, which is that based upon the data presented using the claimed method, the skilled artisan would not reasonably be able to reliably distinguish DNOS patients from other patient populations which are diagnosed as "Alzheimer's Disease" or "possible Alzheimer's Disease" (*see* App. Br. 11, Nagy Dec. ¶¶ 12-15).

Conclusion of Law

The evidence of record supports the Examiner's conclusion that undue experimentation would have been required to perform the claimed diagnostic test for Alzheimer's Disease.

B. 35 U.S.C. § 112, first paragraph, New Matter

The Examiner finds that "[t]here is no mention or teachings of a method step of diagnosing a subject as having one of the neurological conditions recited in claim 1 by merely comparing a G1/S cell cycle checkpoint effectiveness of subject cells to those of 'an individual having said neurological condition'" (Ans. 10). The Examiner finds that there is

"no support for the method step of diagnosing one of the neurological conditions in claim 1 by comparing a determined G1/S cell cycle checkpoint effectiveness with 'the G1/S cell cycle checkpoint effectiveness exhibited by... an individual having said neurological condition'. Thus, the amended claims include impermissible New Matter" (Ans. 10).

Appellant argues that "the Examiner is arguing that no possession of the invention is shown because the exact claim language is not used in the specification, but such argument goes beyond what is required by the law. It is well-settled that the description of a claimed invention need not be in *ipsis verbis*" (App. Br. 13). Appellant argues that the Specification "at page 28, line 11 through page 29, line 3 describes a comparison between patient controls (healthy elderly individuals) and patients with Alzheimer's disease, and then describes an assay based on these results that can be used to diagnose patients at risk for developing Alzheimer' s disease" (*id.*).

In view of these conflicting positions, we frame the New Matter issue before us as follows:

Does the evidence of record support the Examiner's conclusion that Claim 1 fails to comply with the written description requirement as incorporating new matter?

Findings of Fact

20. Claim 1 teaches two alternative modes of diagnosis, one by comparing G1/S cell cycle checkpoint effectiveness of the subject with the effectiveness of a healthy individual and one by comparing effectiveness with an individual having said neurological condition (*see* Claim 1).

21. The Specification teaches that the "presence, of a cell cycle regulatory defect at the G1/S phase transition is indicated by a reduced relative lengthening of the G1 phase in the presence of the cell division inhibitor substance or stimulus in cells from the test subject, as compared to control cells not having a cell cycle regulatory defect at the G1/S phase transition" (Spec. 10, ll. 9-15).

22. The Specification teaches that the "highest values, indicating more effective G1 inhibition by rapamycin, were found in subjects diagnosed as controls, dementia syndromes other than AD and possible Alzheimer's disease patients" (Spec. 26, ll. 6-10).

23. The Specification teaches that the "results of the first set of experiments indicate that G1 inhibitor-induced cell cycle arrest, as indicated by the lengthening of the G1 phase of the cell cycle, is significantly less effective in patients suffering from Alzheimer's disease than in control individuals" (Spec. 28, ll. 11-16).

24. The Specification teaches that

> the results of this study indicate that the response of activated lymphocytes to G1 inhibition is significantly altered in Alzheimer's disease sufferers. In addition these alterations appear early before the onset of a fully developed dementia syndrome identifying subjects who are likely to develop Alzheimer'[s] disease later. The results indicate that a diagnostic test relying on the detection of the integrity of the G1/S transition checkpoint may allow the identification of subjects who are at risk from developing AD later.

(Spec. 29, ll. 25-35.)

Principles of Law

> [T]he hallmark of written description is disclosure. . . . the test requires an objective inquiry into the four corners of the specification from the perspective of a person of ordinary skill in the art. Based on that inquiry, the specification must describe an invention understandable to that skilled artisan and show that the inventor actually invented the invention claimed.

Ariad Pharmaceuticals, Inc. v. Eli Lilly and Co., 598 F.3d 1336, 1351 (Fed. Cir. 2010).

"[T]he written description requirement does not demand either examples or an actual reduction to practice; a constructive reduction to practice that in a definite way identifies the claimed invention can satisfy the written description requirement" *id.* at 1352. "[I]t is the specification itself that must demonstrate possession. And while the description requirement does not demand any particular form of disclosure, . . . or that the specification recite the claimed invention *in haec verba*, a description that merely renders the invention obvious does not satisfy the requirement" *id.* (citations omitted).

It is the Examiner's "initial burden [to] present [ ] evidence or reasons why persons skilled in the art would not recognize in the disclosure a description of the invention defined by the claims." *In re Wertheim*, 541 F.2d 257, 263 (CCPA 1976).

Analysis

There is no dispute that the Specification teaches comparison of the tested non-neuronal cells to controls. The issue is whether the Specification demonstrates possession of a control using cells "of an individual having

said neurological condition" as introduced by Appellant's amendment of August 6, 2007.

Appellant points to page 10 of the Specification, which teaches that the "presence, of a cell cycle regulatory defect at the G1/S phase transition is indicated by a reduced relative lengthening of the G1 phase in the presence of the cell division inhibitor substance or stimulus in cells from the test subject, as compared to control cells not having a cell cycle regulatory defect at the G1/S phase transition" (Spec. 10, ll. 9-15; FF 21). Appellant points to similar teachings throughout the Specification (*see, e.g*, FF 22-24).

However, none of these teachings reasonably suggests or demonstrates possession of the use of affected individuals as positive controls (*see* FF 21-24). While the use of positive controls from affected individuals would reasonably be understood as obvious based upon the disclosure of the Specification, "a description that merely renders the invention obvious does not satisfy the [written description] requirement." *Ariad*, 598 F.3d at 1352.

Conclusion of Law

The evidence of record supports the Examiner's conclusion that Claim 1 fails to comply with the written description requirement as incorporating new matter.

SUMMARY

In summary, we affirm the rejection of claim 1 under 35 U.S.C. § 112, first paragraph, enablement. Pursuant to 37 C.F.R. § 41.37(c) (1)(vii)(2006), we also affirm the rejection of claims 2, 3, 5, 6, 8, 17, 30-32, and 34, as these claims were not argued separately.

We affirm the rejection of claim 1 under 35 U.S.C. § 112, first paragraph, new matter. Pursuant to 37 C.F.R. § 41.37(c) (1)(vii)(2006), we also affirm the rejection of claims 2, 3, 5, 6, 8, 17, 30-32, and 34, as these claims were not argued separately.

No time period for taking any subsequent action in connection with this appeal may be extended under 37 C.F.R. § 1.136(a)(1)(iv)(2006).

AFFIRMED

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